Remarks

Claims 8-11 and 14-16 are pending in the application. Reconsideration and allowance is requested in view of the above changes and the following remarks.

Claims 8, 9 and 16 have been amended to recite that the composition is capable of eliciting both a cytotoxic T-cell and antibody response immune response. Support for the introduction of this feature can be derived from the description at page 14, lines 8-17 and further at page 15, lines 20-27.

Claims 8, 9 and 16 have been amended to recite that the composition comprises a mixture of complexes. Basis for this amendment can be found in the description at page 10, line 22.

Claims 8, 9 and 16 have been amended to recite that the composition comprises a mixture of complexes and that these complexes comprise stress proteins derived from the infected cell *and* the intracellular pathogen, rather than the complexes comprising stress proteins derived from either the infected cell, *or* the intracellular pathogen.

35 USC § 112 – Written Description

Claims 8-11 and 14-16 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement on the basis that written support could not be found by Examiner for the limitation introduced into the claim reading "*eliciting both a cytotoxic and an antibody based immune response*". Applicant respectfully submits that written support in the instant specification is present and does fully support the introduction of this limitation into the claim.

Page 14, lines 8 to 17 state that "*In order to determine the immunogenicity of the SP complexes, T cell proliferation assays may be used*" and further that "*Alternatively, antibody production may be examined ...*". This paragraph of the instant description therefore indicates that immunogenicity can be derived from both T cells and antibodies.

Example 3 of the instant specification (at page 15, lines 20-27) teaches that "*Antibody titres of 1:1-10,000 were routinely obtained and cytotoxic T-cell activity directed against the pathogen infected cells could also be detected in immunised mice*". That specific example further described a challenge experiment, that is, the classical experiment used to show long term protective immunity. The results of the challenge experiment are described as "*Challenge of the rabbits ... at 6, 12 and 18 months periods after the initial immunisations resulted in the production of good antibody responses with titres of 1:1-10 000 indicating good memory responses in the immunised animals*".

Furthermore, page 5, lines 25-28 of the instant specification state that "*A notable aspect of immunity elicited by these induced SPs is the long term memory compared to that induced by immunisation by other SP subsets*".

"The test for determining compliance with the written description requirement is whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language." *In re Kaslow*, 217 USPQ 1089, 1096 (Fed. Cir. 1983), citing *In re Edwards*, 196 USPQ 465 (CCPA 1978). It is clear the applicant had possession of the invention of the amended claims at the time the application was filed. Accordingly, it is respectfully submitted that the instant specification provides adequate written support for the composition of the claims "*eliciting both a cytotoxic and an antibody based immune response*".

35 USC § 102

Response to Section 102 Rejection over Srivastava (WO 95/24923)

Claims 8-11 and 14-16 have been rejected as allegedly anticipated by Srivastava WO 95/24923.

The applicant respectfully submits that the claims of the instant application are not anticipated by the teaching of Srivastava.

Cited art does not mediate an antibody response

Srivastava makes no mention of the compositions disclosed therein mediating both a cytotoxic T-cell and an antibody based immune response. Specifically, although a cytotoxic T cell response is assessed, there is no mention of an antibody or humoral immune response being mediated by the compositions. Example 3 (page 15, lines 20 to 27) and Example 5 (page 18, lines 10-12) of the instant specification specifically refer to and quantify the antibody titre produced in subjects immunized with compositions of the present invention. Page 46, lines 4-7 of Srivastava refer to the administration of the complexes of Srivastava to an animal to stimulate a cytotoxic T cell response. Srivastava is wholly silent as to the productions of an antibody (humoral) immune response, resulting from the administration of the complexes.

Specifically WO95/24923 of Srivastava is silent in relation to the elicitation of humoral immune responses in the subject. It is clear from a reading of Srivastava that the compositions used therein are for the elicitation of cell mediated CTL responses only. Indeed, Srivastava is littered with statements to that effect.

For example page 9, lines 4-9 of WO95/24923 states that "*It has now been discovered that a subunit vaccine containing a stress protein peptide complex when isolated from cells infected with a pre-selected pathogen intracellular pathogen and then administered to a mammal can effectively stimulate cellular immune responses against cells infected with the same pathogen. Specifically, the immune response is mediated through the cytotoxic T cell cascade*". Similarly, at page 9, lines 21-22 of WO95/24923, Srivastava states that the preferred embodiment of both inventions comprises "*a vaccine that can be administered to a mammal for inducing in the mammal a cytotoxic T cell response*", and that "*The vaccines manufactured in accordance with the principles described herein contain an immunogenic stress protein-peptide*

complex that is capable of stimulating in the recipient a cytotoxic T cell response" at page 9, lines 25-29.

Moreover, all remaining embodiments of the inventions described throughout both Srivastava documents stipulate that the immune response generated is a cytotoxic T cell response. Other examples from WO95/24923 can be found at page 13, lines 1, 9, 12 and 14; at page 14, lines 5-9 which stipulate that "*the vaccine stimulates the cytotoxic T cell response via the major histocompatability complex (MHC) class I cascade*", which results in CTL responses only; at page 14, lines 12, 16 and 19; and at page 15, lines 12-15. Thus, all contemplated embodiments of the inventions taught by WO95/24923 of Srivastava are silent on the generation of humoral antibody responses and are concerned with the induction of cell mediated CTL immune responses only.

Multiple complexes present in present invention

Claim 8 of the instant application recites that the stress protein complexes are derived from the infected cell and also from the intracellular pathogen. Srivastava does not provide such complexes. Srivastava provides only complexes derived from the infected cell. Page 20, lines 21-23 of Srivastava teaches that "The immunogenic complexes may be purified from any eukaryotic cells...". Page 19, lines 4-8 of Srivastava state that "The invention is based on the discovery that a stress protein-peptide complex isolated from a eukaryotic cell infected with a preselected intracellular pathogen...". Srivastava does state at Page 11, lines 1 and 2 that "Stress proteins are found in all prokaryotes and eukaryotes and exhibit a remarkable level of evolutionary conservation". However, this discussion of non-eukaryotic stress proteins included in Srivastava is only for the purpose of providing general background information on stress proteins. It is respectfully submitted that this mention of prokaryotes was not intended to mean that Srivastava considered that stress protein complexes could be derived from prokaryotic cells for use in the invention. That is simply not the case. For example, at page 25, lines 9-12 of Srivastava, it is stated that "As will be appreciated by those skilled in the art, the protocols described herein may be used to isolate stress protein-peptide complexes from any *eukaryotic*

cell." There is no teaching of how to isolate stress proteins from prokaryotic cells or other intracellular pathogens which may be infecting the eukaryotic cells as this is simply not envisaged by Srivastava.

Complexes of cited art comprise only eukaryotic stress proteins

Furthermore, the inherent inclusion of stress proteins derived from prokaryotes in the complexes of Srivastava would simply not occur. Page 27, line 4 onwards of Srivastava teach the procedure for "Preparation of Stress Proteins and Immunogenic Stress Protein-Peptide Complexes". Page 27, lines 13 onwards set out the procedure for the initial purification of cells. No detergent is used in the buffer, hence the buffer described would not lyse the cell walls of any intracellular pathogens contained within the eukaryotic cells.

Furthermore, Srivastava also employs the use of a dounce homogenizer to rupture cells. However, again, this would not result in the rupturing of the cell walls of any intracellular pathogens contained within the eukaryotic bacteria of Srivastava. The fact that neither the buffer conditions nor the dounce homogenizer conditions set forth in Srivastava would break up the cell wall of an intracellular pathogen infecting a eukaryotic cell in Srivastava is entirely expected by Srivastava. Specifically, at page 27, lines 22-24, Srivastava teaches that "The lysate is centrifuged at 1000 g for 10 minutes to remove unbroken cells". These cells would of course not be eukaryotic cells, as it would not be desirable for Srivastava to teach that any unbroken eukaryotic cells were to be discarded as these cells would have complexes in them which could be used in the compositions of Srivastava. Hence, Srivastava would not purposefully discard unbroken eukaryotic cells. Rather, these unbroken cells would be intracellular pathogens found within the lysed eukaryotic cell. It was the clear intention of Srivastava to retain these (intracellular pathogen) cells in an intact form, collect them and discard them. Accordingly, Srivastava does not teach of the use of stress proteins derived from both eukaryotic cells and intracellular pathogens, as the methodology and teaching of Srivastava does not disclose such a combination of complexes.

Further support for the above argument, as well as a detailed technical explanation as to why the conditions disclosed in Srivastava would not result in the rupturing of intracellular pathogens, and the associate release of their stress proteins into the complexes of Srivastava, was included in the Applicant's response to the office action of February 10, 2009. Specifically, the method of production of the stress protein-peptide complexes disclosed in the instant application as filed employs the use of a dounce homogenizer *and a buffer comprising the detergent Tween* (see Example 1, page 13, lines 1-6 of the application as filed). In this example, upon disruption of the host cells the detergent would efficiently solubilize the endosomal membranes and those of the intracellular pathogen contained therein, resulting in the release of pathogen-derived stress protein-peptide complexes *in addition to* host cell-derived stress protein-peptide complexes into the lysate. Similarly, Example 2 of the application as filed discloses the use of a dounce homogenizer; cycles of freeze-thaw or detergent lysis (see Example 2, page 15, lines 1-3 of the application as filed). Example 5 details the use of disruption of infected host cells with 1 % Tween detergent solution (see Example 5, page 17, and lines 22-24 of the application as filed). Hence, these methods would also result in the liberation of pathogen-derived as well as host-cell derived stress protein-peptide complexes into the lysate, as both the detergent and freeze-thaw techniques are capable of lysing intra-cellular pathogens within host cells.

Thus in all embodiments of the instant invention, the pooling of pathogen-derived and host-derived stress proteins is disclosed, and the stress protein/antigenic peptide fragment complexes of the instant claims would comprise a mixture of pathogen derived and host cell derived stress protein families. Such a mixture, which has been explicitly set forth in the claims as amended, is not taught by Srivastava.

In the response to applicant's arguments, Examiner states that "*The claims [of the instant application] do not require the use of more than one stress peptide. In fact the claims recite the complex is between a stress induced protein and an antigenic determinant*". This statement is generally correct, in that a stress protein-peptide complex can only contain a *single* stress protein. However, Examiner is incorrect in referring to a "complex". The claims recite "complexes"; that is, a *plurality* of complexes. Each complex will be formed from a different combination of a stress protein and an antigenic peptide fragment. As set out in claim 8, the stress protein can be

derived from the infected cell (*i.e.*, the stress protein is derived from a eukaryotic cell and therefore is a eukaryotic stress protein), or the stress protein can be derived from the intracellular pathogen itself (*i.e.*, the stress protein is a bacterial, protozoal or parasitic intracellular pathogen derived stress protein).

Applicant therefore respectfully submits that, contrary to Examiner's assertions, there is a structural difference between the product claimed and the product taught by the prior art.

Response to Section 102 Rejection over Srivastava (US 5,961,979)

Claims 8-11 and 14-16 have been rejected as allegedly anticipated by Srivastava US 5,961,979.

The applicant respectfully submits that the claims of the instant application are not anticipated by the teaching of Srivastava.

Cited art does not mediate an antibody response

Srivastava makes no mention of the compositions disclosed therein mediating both a cytotoxic T-cell and an antibody based immune response. Specifically, although a cytotoxic T cell response is assessed, there is no mention of an antibody or humoral immune response being mediated by the compositions. Example 3 (page 15, lines 20 to 27) and Example 5 (page 18, lines 10-12) of the instant specification, on the other hand, specifically refer to and quantify the antibody titre produced in subjects immunized with compositions of the present invention. Column 22, lines 49-53 of Srivastava refer to the administration of the complexes of Srivastava to an animal to stimulate a cytotoxic T cell response. Srivastava is wholly silent as to the productions of an antibody (humoral) immune response, resulting from the administration of the complexes.

Specifically Srivastava is silent in relation to the elicitation of an antibody mediated humoral immune responses in the subject. It is clear from a reading of Srivastava that the compositions used therein are for the elicitation of cell mediated CTL responses only. For

example column 4, lines 55-68 states that "*It has now been discovered that a subunit vaccine containing a stress protein peptide complex when isolated from cells infected with a pre-selected pathogen intracellular pathogen and then administered to a mammal can effectively stimulate cellular immune responses against cells infected with the same pathogen. Specifically, the immune response is mediated through the cytotoxic T cell cascade*". Similarly, at column 5, lines 5-7 of Srivastava states that the preferred embodiment of both inventions comprises "*a vaccine that can be administered to a mammal for inducing in the mammal a cytotoxic T cell response*", and that "*The vaccines manufactured in accordance with the principles described herein contain an immunogenic stress protein-peptide complex that is capable of stimulating in the recipient a cytotoxic T cell response*" at column 5, lines 11-14. Moreover, all remaining embodiments of the inventions described throughout Srivastava stipulate that the immune response generated is a cytotoxic T cell response. Other examples can be found at column 6, lines 54 and 65; at column 7, lines 2 and 5; at column 7, lines 30-35 which stipulate that "*the vaccine stimulates the cytotoxic T cell response via the major histocompatability complex (MHC) class I cascade*", which results in CTL responses only; at column 7, lines 38, 43-44, and 45-52; and at column 8, lines 6-12.

Thus, all contemplated embodiments of the inventions taught by Srivastava are silent on the generation of humoral antibody responses and are concerned with the induction of cell mediated CTL immune responses only.

Multiple complexes present in present invention

Claim 8 of the instant application recites that the stress protein complexes are derived from the infected cell and also from the intracellular pathogen. Srivastava does not provide such complexes. Srivastava provides only complexes derived from the infected cell. Column 10, line 27 of Srivastava teaches that "The immunogenic complexes may be purified from any eukaryotic cells...". Column 9, lines 24 and 25 of Srivastava state that "The invention is based on the discovery that a stress protein-peptide complex isolated from a eukaryotic cell infected with a preselected intracellular pathogen...". Srivastava does state at column 5, lines 55 and 56 that

"Stress proteins are found in all prokaryotes and eukaryotes and exhibit a remarkable level of evolutionary conservation". However, this discussion of non-eukaryotic stress proteins is included in Srivastava is only for the purpose of providing general background information on stress proteins. It is respectfully submitted that this mention of prokaryotes was not intended to mean that Srivastava considered that stress protein complexes could be derived from prokaryotic cells for use in his invention. That is simply not the case. For example, at column 12, lines 55-58 of Srivastava, it is stated that "As will be appreciated by those skilled in the art, the protocols described herein may be used to isolate stress protein-peptide complexes from any *eukaryotic* cell." There is no teaching of how to isolate stress proteins from prokaryotic cells or other intracellular pathogens which may be infecting the eukaryotic cells as this is simply not envisaged by Srivastava.

Complexes of cited art comprise only eukaryotic stress proteins

Furthermore, the inherent inclusion of stress proteins derived from prokaryotes in the complexes of Srivastava would simply not occur. Column 13, lines 51 onwards of Srivastava teach the procedure for "Preparation of Stress Proteins and Immunogenic Stress Protein-Peptide Complexes". Lines 54 to 63 of column 13 set out the procedure for the initial purification of cells. No detergent is used in the buffer, hence the buffer described would not lyse the cell walls of any intracellular pathogens contained within the eukaryotic cells.

Furthermore, Srivastava also employs the use of a dounce homogenizer to rupture cells. However, again, this would not result in the rupturing of the cell walls of any intracellular pathogens contained within the eukaryotic bacteria of Srivastava. The fact that neither the buffer conditions nor the dounce homogenizer conditions set forth in Srivastava would break up the cell wall of an intracellular pathogen infecting a eukaryotic cell in Srivastava is entirely expected by Srivastava. Specifically, at column 13, lines 64 and 65, Srivastava teaches that "The lysate is centrifuged at 1000 g for 10 minutes to remove unbroken cells". These cells would of course not be eukaryotic cells, as it would not be desirable for Srivastava to teach that any unbroken eukaryotic cells were to be discarded, as these cells would have complexes in them which could

be used in the compositions of Srivastava. Hence, Srivastava would not purposefully discard unbroken eukaryotic cells. Rather, these unbroken cells would be intracellular pathogens found within the lysed eukaryotic cell. It was the clear intention of Srivastava to retain these (intracellular pathogen) cells in an intact form, collect them and discard them. Accordingly, Srivastava does not teach of the use of stress proteins derived from both eukaryotic cells and intracellular pathogens as the methodology and teaching of Srivastava does not disclose such a combination of complexes.

Further support for the above argument, as well as a detailed technical explanation as to why the conditions disclosed in Srivastava would not result in the rupturing of intracellular pathogens, and the associated release of their stress proteins into the complexes of Srivastava, was included in the Applicant's response to the office action of February 10, 2009. Specifically, the method of production of the stress protein-peptide complexes disclosed in the instant application as filed employs the use of a dounce homogenizer *and a buffer comprising the detergent Tween* (see Example 1, page 13, lines 1-6 of the application as filed). In this example, upon disruption of the host cells the detergent would efficiently solubilize the endosomal membranes and those of the intracellular pathogen contained therein, resulting in the release of pathogen-derived stress protein-peptide complexes *in addition to* host cell-derived stress protein-peptide complexes into the lysate. Similarly, Example 2 of the application as filed discloses the use of a dounce homogenizer; cycles of freeze-thaw or detergent lysis (see Example 2, page 15, lines 1-3 of the application as filed). Example 5 details the use of disruption of infected host cells with 1 % Tween detergent solution (see Example 5, page 17, and lines 22-24 of the application as filed). Hence, these methods would also result in the liberation of pathogen-derived as well as host-cell derived stress protein-peptide complexes into the lysate, as both the detergent and freeze-thaw techniques are capable of lysing intra-cellular pathogens within host cells.

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In the response applicant's arguments, Examiner states that "*The claims [of the instant application] do not require the use of more than one stress peptide. In fact the claims recite the complex is between a stress induced protein and an antigenic determinant*". This statement is generally correct, in that a stress protein-peptide complex can only contain a *single* stress protein. However, Examiner is incorrect in referring to a "complex". The claims recite "complexes"; that is a *plurality* of complexes. Each complex will be formed from a different combination of a stress protein and an antigenic peptide fragment. As set out in claim 8, the stress protein can be derived from the infected cell (*i.e.*, the stress protein is derived from a eukaryotic cell and therefore is a eukaryotic stress protein), or the stress protein can be derived from the intracellular pathogen itself (*i.e.*, the stress protein is a bacterial, protozoal or parasitic intracellular pathogen derived stress protein).

Applicant therefore respectfully submits that, contrary to Examiner's assertions, there is a structural difference between the product claimed and the product taught by the prior art.

Status of Other Applications of Applicant Directed to Related Subject Matter

Application No. 10/049,704. The '704 application was subject to an office action dated December 12, 2008. A response to that action was filed on June 12, 2009.

Application No. 10/363,454 (US-2005-0232946): The '704 application was subject to an office action dated June 2, 2009. Applicant responded to the office action on Dec. 4, 2009. A further office action issued on February 19, 2010. Applicant not yet responded to the office action.

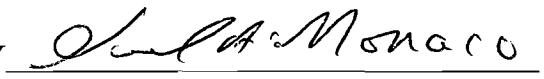
To complete the record, copies of the office actions from the above-identified applications, and from the file of abandoned application 10/204,828, are submitted herewith under cover of an Information Disclosure Statement and PTO Form 1449. The present application was the subject of an obviousness-type double patenting rejection in an office action dated Feb. 21, 2006 in application 10/204,828. That rejection was withdrawn when the allegedly conflicting claims were cancelled in the present application.

Conclusion

The claims of the application are believed in condition for allowance. An early action toward that end is earnest solicited.

Respectfully submitted

CAMILO ANTHONY LEO SELWYN COLACO

BY 

DANIEL A. MONACO
Reg. No. 30,480
DRINKER, BIDDLE & REATH, LLP.
One Logan Square, Suite 2000
Philadelphia, PA 19103-6996
(215) 988-3312
(215) 988-2757 – fax
Attorney for the Applicant